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Title: Method for the preparation of escitalopram

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05 August 2003

Bo Z. Tidemann

PATENT- OG VAREMÆRKESTYRELSEN

Method for the preparation of escitalopram.

The present invention relates to a novel method for the preparation of escitalopram involving selective enzymatic acylation or deacylation of an intermediate in the preparation of escitalopram.

Background of the invention

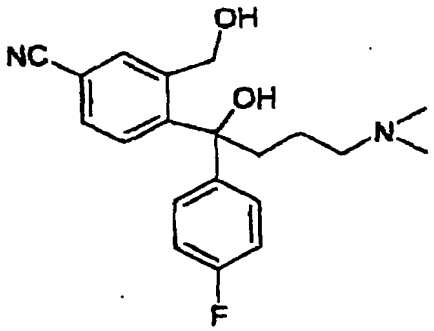
Citalopram is a well-known antidepressant drug that has now been on the market for some years.

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication i.a. outlines a process for preparation of citalopram from the corresponding 5-bromo-derivative by reaction with cuprous cyanide in a suitable solvent.

US Patent No 4,943,590 corresponding to EP-B1-347 066 describes two processes for the preparation of the escitalopram (S-enantiomer of citalopram).

Both processes use the racemic diol having the formula



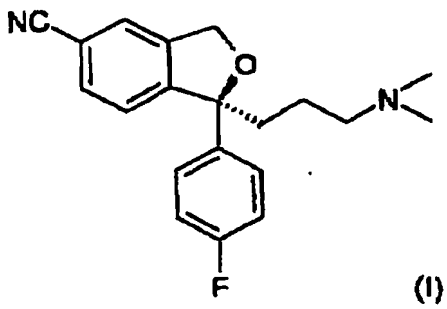
(A)

as starting material. According to the first process, the diol of formula (A) is reacted with an enantiomerically pure acid derivative, such as (+) or (-)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride to form a mixture of diastereomeric esters, which are separated by HPLC or fractional crystallization, whereupon the ester with the correct stereochemistry is enantioselectively converted into escitalopram. According to the second process, the diol of formula (A) is separated into the enantiomers by stereoselective crystallization with an enantiomerically pure acid such as (+)-di-*p*-toluoyltartaric acid, whereupon the S-enantiomer of the diol of the formula (A) is enantioselectively converted to escitalopram.

Escitalopram has now been developed as an antidepressant. Hence, there is a desire for an improved method for preparation of escitalopram.

The present invention

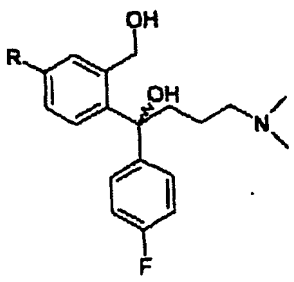
Accordingly, the present invention relates to a novel process for the preparation of escitalopram having the formula



(I)

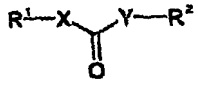
or a pharmaceutically acceptable salt thereof comprising

a) subjecting a compound of formula



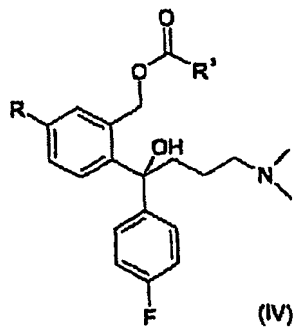
(II)

wherein R is cyano or a group which may be converted to a cyano group to enzymatic acylation in presence of a hydrolase using an acylating reagent having the formula



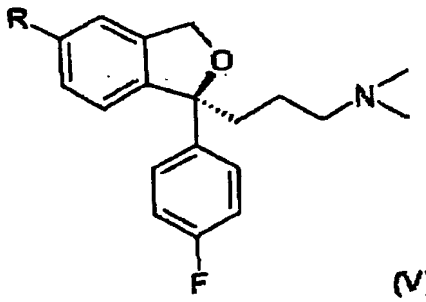
(III)

wherein X is a bond, O, S, NH, or NR^0; R^0 and R^1 are independently C_{1-8}-alkyl, C_{2-8}-alkenyl or C_{2-8}-alkynyl which may optionally be substituted with C_{1-8}-alkoxy, C_{1-8}-alkylthio, halogen, C_{1-8}-alkylamino or di-(C_{1-8}-alkyl)amino, or aryl or heteroaryl; Y is ~~O, S, O-CO, or S-CO; and R^2 is C_{1-8}-alkyl, C_{2-8}-alkenyl or C_{2-8}-alkynyl which may~~ optionally be substituted with C_{1-8}-alkoxy, C_{1-8}-alkylthio, halogen, C_{1-8}-alkylamino or di-(C_{1-8}-alkyl)amino, or aryl or heteroaryl; provided that X is not S or O when Y is O-CO or S-CO and X is not S when Y is S; or R^1 and R^2 together form a cyclic structure; to form a mixture of the starting material of formula (II) in either the R- or S-form and the acylated form of the other enantiomer having the formula



(IV)

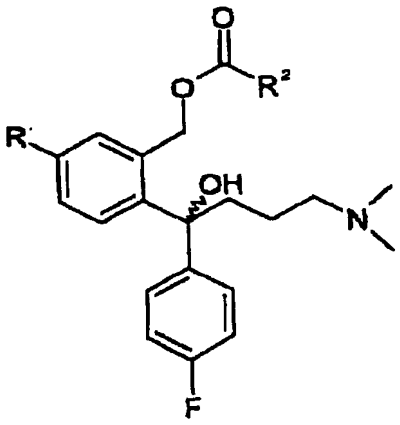
wherein R is as defined above and $-CO-R^3$ is a group resulting from acylation of a compound (II) with a compound of formula (III); and if R is not cyano optionally followed by conversion of the group R to a cyano group and then conversion of the S-enantiomer of formula (II) or (IV) to a compound of formula



(V)

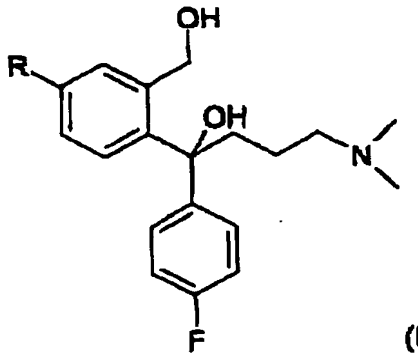
and if R is not cyano conversion of the group R to a cyano group and isolation of escitalopram or a pharmaceutically acceptable salt thereof; or

b) subjecting a compound of formula



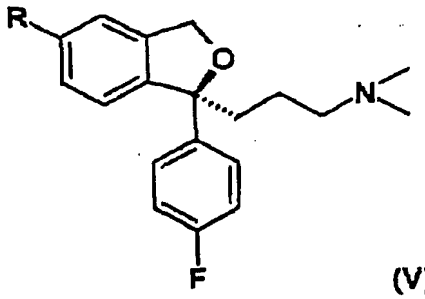
(VI)

wherein R and R^2 are as defined above; to selective enzymatic deacylation in presence of a hydrolase and water to form a mixture of deacylated compound of formula



(II)

wherein R is cyano or a group which may be converted to a cyano group in either the R- or the S-form and the acylated starting material of formula (VI) in the form of the opposite enantiomer; and if R is not cyano optionally followed by conversion of R to cyano and then conversion of the S-enantiomer of formula (II) or (VI) to a compound of formula



(V)

and if R is not cyano conversion of the group R to a cyano group and isolation of escitalopram or a pharmaceutically acceptable salt thereof.

In one embodiment of the invention, the acylation of the compound of formula (II) results in a mixture of a compound of formula (II) in the S-form and the compound of formula (IV) in the R-form.

In a second embodiment of the invention, the acylation of the compound of formula (II) results in a mixture of a compound of formula (II) in the R-form and the compound of formula (IV) in the S-form.

In a third embodiment of the invention the deacylation of the compound of formula (VI) results in a mixture of a compound of formula (VI) in the S-form and the compound of formula (II) in the R-form.

In a fourth embodiment of the invention the deacylation of the compound of formula (VI) results in a mixture of a compound of formula (VI) in the R-form and the compound of formula (II) in the S-form.

According to preferred embodiments of the invention, R is cyano, X is a bond, R^1 is C_{1-8}-alkyl, preferably methyl, ethyl, propyl, isopropyl or butyl, Y is O or O-CO R^2 in the compound of formula (III) is C_{2-8}-alkene, preferably vinyl or 1-methyl-vinyl, R^3 is C_{1-8}-alkyl, preferably methyl, ethyl, propyl, isopropyl and butyl and/or R^2 in the compound of formula (VI) is C_{1-8}-alkyl, preferably methyl, ethyl, propyl, isopropyl and butyl.

Detailed description of the invention

According to the invention, selective enzymatic acylation/deacylation means that the enzymation acylation or deacylation is preferentially effective for conversion of one of the enantiomers of a compound of formula (II) or (VI) respectively leaving the other enantiomer of the compound of formula (II) or (VI) as unconverted in the reaction mixture.

The mixtures obtained according to the invention may not be entirely pure, for example they may contain a smaller amount of the other enantiomer of any of the compounds of formula (II), (IV), (V) and (VI) in addition to a larger amount of the specific enantiomer obtained according to the invention.

The mixture obtained after acylation or deacylation according to the invention depend on the specific hydrolase used and the conditions under which the reaction is carried out.

Suitable hydrolases for carrying out acylation of the compounds of formula (II) and deacylation of compounds of the formula (VI) are for example:

Acylase I (AA) (from Aspsergillus melleus or hog kidney(HKA)),

Acylase I , immobilized on Eupergit C,

Esterase (from Bacillus sp. (e.g. stearothermophilus; thermoglucosidasius; lipolytica)),

PLE (pig liver esterase),

PLE immobilized on Eupergit C,

HLE (horse liver esterase),

Esterases (from Mucor miehei; Saccharomyces cerevisiae; Thermoanaerobium brockii),

Esterase Isoenzyme 1 (from hog liver),

CHE (Cholesterol esterase),

AchE (Acetylcholine esterase),

ACL (Achromobacter sp. Lipase),

Lipase (from Aspergillus sp. (e.g. niger (ANL); oryzae),

Lipase from Aspergillus sp. immobilized or recombinant,

Lipase from Candida Antarctica,

Lipase from Candida antarctica (immobilized or recombinant),

CCL (Candida cylindracea lipase),

CCL, immobilized in Sol-Gel-AK,

Lipase (Lipases from Candida lipolytica or candida utilis),

PPL (Porcine pancreatic lipase),

PPL, immobilized,

Lipase from Mucor sp. (meihei (MML); javanicus),

Lipase from Mucor sp. immobilized or recombinant,

Lipase from pinicillium roqueforti,

PSL, Lipase from Pseudomonas sp. (e.g. aeruginosa (PAL); cepacia; fluorecens (PFL))

PSL, immobilized,

Lipase from Rhizomucor miehei,

Lipase from Rhizopus sp. (arrhizus (RAL); delemar; japonicus; niveus),

Lipase from Thermus sp. (aquatius; flavus; thermophilus),

TVL (Trichoderma viridae Lipase),

Lipase from wheat germ,

HRL (Humicola ramingera lipase),
CVL (Chromobacterium viscosum lipase),
Lipozyme ™,
Subtilisin from bacillus licheniformis (Alcalase),
Subtilisin from bacillus licheniformis,
Proteinase from Aspergillus sp.,
Proteinase from bacillus subtilis,
Subtilisin Carlsberg (STC),
Proteinase K,
Proteinase K, immobilised,
Proteinase N,
Proteinase, bacterial origin,
Papain from Carica papaya (PP),
Papain, immobilized on Eupergit C,
Trypsin from bovine or hog pancreas (TR) and
alfa-Chymotrypsin from bovine pancreas (CTR). In particular immobilised forms of the enzymes above or Clec enzymes are useful according to the invention.

Preferred hydrolases are PLE, HLE, PPL, CCL, PFL, PSL, CVL, MML, TVL, alfa-Chymotrypsin, Subtillisin, Trypsin, Papain, Acylase I (pig kidney or aspergillus subtilis), lipozyme™ and penicillin acylase, preferably in immobilised form.

The most preferred hydrolases are PPL, PLE, Papain, CCL or lipozyme ™, preferably in immobilised form.

Selective enzymatic acylation is preferably carried out in an almost anhydrous organic solvent in presence of a hydrolase (enzymes normally requires the presence of some water to be active). Suitable organic solvent for enzymatic acylation are organic solvents such as toluene, hexane, heptane, dioxane and THF. The skilled person wil be able to identify other suitable solvents.

Selective enzymatic deacylation is preferably carried out in water or a mixture of water and an organic solvent and a hydrolase. Suitable organic solvents are solvents

such as acetonitrile, DMF, DMSO, dioxane, DME and diglyme. The skilled person will be able to identify other suitable solvents.

The preferred reaction conditions for enzymatic acylation/deacylation differ depending on the particular enzyme used, whether it is immobilised or not etc. Reaction conditions such as pH, temperature, the use of additives, such as for example salts, amines, phase transfer catalysts (e.g. quaternary ammonium compounds) and polyethylene glycols, may be identified by a person skilled in the art.

Ring-closure of a compound of formula (IV), (VI) or a labile ester derivative of the compound of formula (II) to form the compound of formula (V) may suitably be carried out by treatment of the compound with a base such as $KOC(CH_3)_3$ and other alkoxides, NaH and other hydrides, triethylamine, ethyldiisopropylamine or pyridine in an inert organic solvent, such as tetrahydrofuran, toluene, DMSO, DMF, t-butyl methyl ether, dimethoxyethane, dimethoxymethane, dioxane, acetonitrile or dichloromethane. The more labile the acyl group -CO-R^3 in the compound of formula (IV), the acyl group –CO-R^2 in the compound of formula (VI) and the ester group in the labile ester derivative of the compound of formula (II) is, the weaker the strength of the base needs to be. When the acyl group -CO-R^3 in the compound of formula (IV) and the acyl group –CO-R^2 in the compound of formula (VI) is not very labile a stronger base has to be used in connection with the ring-closure.

This process has already been described in US patent No. 4,943,590.

In some cases, it may be advantageous to exchange the group -O-CO-R^3 or -O-CO-R^2 in the compounds of formula (IV) and the compound of formula (VI) respectively, for a more labile group before ringclosure is carried out. Such labile groups (leaving groups) could typically be a group selected from methanesulfonyloxy, *p*-toluenesulfonyloxy, 10-camphorsulfonyloxy, trifluoroacetyloxy and trifluoromethanesulfonyloxy or halogen.

Typically, the compound of formula (IV) or (VI) is subjected to hydrolysis to form a compound of formula (II) with aquesous base, such as NaOH, KOH or LiOH in water or alcohol or a mixture thereof and then reacted with an activated leaving group, such

as for example mesylchloride ot tosylchloride in an organic solvent in the presence of an organic base.

The compounds of formula (II) and (IV) and the compounds of formula (II) and (VI) obtained according to the invention may be separated before conversion of the S form of either compound (II), (IV) or (VI) to escitalopram.

The S-form of a compound of formula (II), (IV) or (VI) may also be converted to escitalopram before it is separated from the R-form of (II), (IV) or (VI) contained in the mixture after acylation or deacylation.

Separation of the compounds of formula (II), (IV), (V) and (VI) from each other may be carried out by crystallisation, phase separation or chromatography using conventional methods.

The optical purity of the product obtained after separation of the compounds of formula (II) and (IV) or (VI) may have to be improved before ring-closure. Improvement of the optical purity may be obtained by chromatography as described in International patent application No. PCT/DK02/00491 or by crystallisation of diastereomeric esters or salts with optically active acids as described in US patent No. 4,943,590.

Likewise, the optical purity of the escitalopram product may have to be improved. Improvement of the optical purity may be obtained by chromatography on a chiral stationary phase.

As used herein, the term C_{1-8}-alkyl refers to a branched or unbranched alkyl group having from one to eight carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl. C_{1-6}-alkyl refers to the same groups as C_{1-8}-alkyl but contain only up to six carbon atoms.

Similarly, C_{2-8}-alkenyl and C_{2-8}-alkynyl, respectively, designate such groups having from two to eight carbon atoms, including one double bond and one triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The terms C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylamino, etc. designate such groups in which the alkyl group is C_{1-8} alkyl as defined above.

Halogen means fluoro, chloro, bromo or iodo.

The term aryl refers to a carbocyclic aromatic group, such as phenyl, or naphthyl, in particular phenyl. The aryl group may be substituted with groups such as C_{1-8}-alkyl, C_{2-8}-alkenyl , C_{2-8}-alkynyl, C_{1-8}-alkoxy, C_{1-8}-alkylthio, halogen, C_{1-8}-alkylamino and di-(C_{1-8}-alkyl)amino as well as other small substitutents.

The term heteroaryl refers to monocyclic or polycyclic heteroaromatic groups. The heteroaryl group may be substituted with groups such as C_{1-8}-alkyl, C_{2-8}-alkenyl , C_{2-8}-alkynyl, C_{1-8}-alkoxy, C_{1-8}-alkylthio, halogen, C_{1-8}-alkylamino and di-(C_{1-8}-alkyl)amino as well as other small substitutents.

R^1 and R^2 may together with –X-CO-Y- where X and Y is as defined above, form a cyclic structure such as a cyclic lactone, a carbonate or an anhydride.

As mentioned above, the group R means cyano or any other group which may be converted to a cyano group.

Groups which may be converted to a cyano group include halogen such as chloro, bromo, iodo or fluoro, preferably chloro or bromo.

Other groups which may be converted to cyano include CF_3-$(CF_2)_n$-SO_2-O- , wherein n is 0-8, -OH, -CHO, -CH_2OH, -CH_2NH_2, -CH_2NO_2, -CH_2Cl, -CH_2Br, -CH_3, -NHR^4, -CHNOH, -$COOR^5$, -$CONR^6R^7$ wherein R^4 is hydrogen or alkylcarbonyl, and R^6 and R^7 are selected from hydrogen, optionally substituted alkyl, aralkyl or aryl and, a group of formula

(VII)

wherein Z is O or S; $R^8 - R^9$ are each independently selected from hydrogen and C_{1-6} alkyl or R^8 and R^9 together form a C_{2-5} alkylene chain thereby forming a spiro ring; R^{10} is selected from hydrogen and C_{1-6} alkyl, R^{11} is selected from hydrogen, C_{1-6} alkyl, a carboxy group or a precursor group therefore, or R^{10} and R^{11} together form a C_{2-5} alkylene chain thereby forming a spiro ring.

When R is halogen, in particular bromo or chloro, conversion of the compound of formula (V) to form escitalopram may be carried out as described in US 4,136,193, WO 00/13648, WO 00/11926 and WO 01/02383.

According to US 4,136,193 conversion of the 5-bromo group in a compound corresponding to the compound of formula (V) to a cyano group, is carried out by reaction with CuCN.

WO 00/13648 and WO 00/11926 describe the conversion of a 5-halogen or a triflate group in a compound corresponding to the compound of formula (V) to a cyano group by cyanation with a cyanide source in presence of a Pd or Ni catalyst.

Other processes for the conversion of a 5-bromo compound of formula (V) to the corresponding 5-cyano derivative involve reaction of 5-bromocitalopram with magnesium to form a Grignard reagent, followed by reaction with a formamide to form an aldehyde. The aldehyde is converted to an oxime or a hydrazone which is converted to a cyano group by dehydration and oxidation, respectively.

Alternatively, 5-bromo-citalopram of formula (V) is reacted with magnesium to form a Grignard reagent, followed by reaction with a compound containing a CN group bound to a leaving group.

A detailed description of the above two procedures may be found in WO 01/02383.

Compounds of formula (V), wherein the group R is –CHO, may be converted to escitalopram by methods analogous to those described in WO 99/00210.

Compounds of formula (V), wherein the group R is NHR^{12}, wherein R^{12} is hydrogen or alkylcarbonyl, may be converted to escitalopram by methods analogous to those described in WO 98/19512.

Compounds of formula (V), wherein the group R is $-CONR^{13}R^{14}$, wherein R^{13} and R^{14} are selected from hydrogen optionally substituted alkyl, aralkyl or aryl may be converted to escitalopram by methods analogous to those described in WO 98/00081 and WO 98/19511.

Compounds of formula (V), wherein the group R is a group of formula (VII) may be converted to escitalopram by methods analogous to those described in WO 00/23431.

Compounds of formula (V), wherein X is OH, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NO_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_3$ or any of the groups above, may be converted to escitalopram by methods analogous to those described in WO 01/168632.

Starting materials may be prepared according to the above mentioned patents and patent applications or by analogous methods.

Escitalopram of formula (I) may be used as the free base or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

Example 1

General procedure for the kinetic resolution of citalopram diol (II) systems

To a stirred solution of racemic diol (II) (0.1 mol) and an acylating agent (0.2 – 0.3 mole)(given in the description; e.g. a vinyl acylate or an aryl acylate) in a dry solvent (e.g. toluene, THF or heptane) (1 L) under a nitrogen atmosphere is added the enzyme (hydrolase (aprox. 5 grams) (e.g. an esterase (PLE), acylase (acylase I) or lipase (lipozyme™))). The reaction mixture is heated to 30 – 70 °C and followed by HPLC (Chiralcel column) or super critical fluid chromatography. The separation/enantiomeric excess is compared with authentic samples of the corresponding R or S isomers of the diol systems. When the reaction has reached the desired degree of acylation the enzyme is filtered off and washed with a small amount of the solvent used. The combined organic phases are evaporated *in vacuo* and the two isomers are separated (crystallisation, phase separation or column chromatography) and isolated. The S-enantiomer is converted into Escitalopram.

Example 2

General procedure for the kinetic resolution of acylated citalopram diol (VI) systems

To a well stirred solution of racemic acylated diol (VI) (0.1 mol) in water, pH = 7.2 by addition of 1 N HCl, and a organic cosolvent (0-50%) (e.g. THF, diglyme, dioxane, DMF or acetonitrile) (1-4 L) is added the enzyme (hydrolase (aprox. 2-4 portions of 5

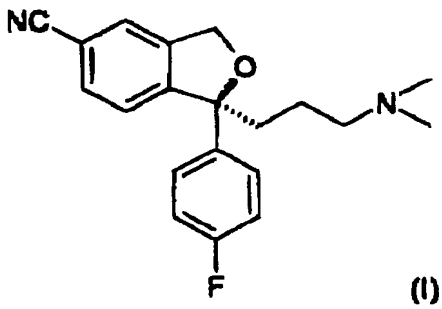
grams over the reaction time (2-48 hours) (e.g. an esterase (PLE), an acylase (acylase I) or a lipase (lipozyme))) at 25 °C.

The pH of the reaction mixture is kept at 7-8 by addition of 2 N NaOH via a pH stat (syringe pump interfaced with a pH controller) The reaction mixture is kept at 25-35 °C and followed by HPLC (Chiralcel column) or super critical fluid chromatography. The separation/enantiomeric excess is compared with authentic samples of the corresponding R or S isomers of the diol systems. When 0.05 mole of the aqueous 2 N NaOH is added the enzyme is eliminated by filtration.

The reaction mixture is extracted by toluene and the combined organic phases are evaporated *in vacuo* and the two isomers are separated (crystallisation, phase separation or column chromatography) and isolated. The S-enantiomer is converted into Escitalopram.

Claims:

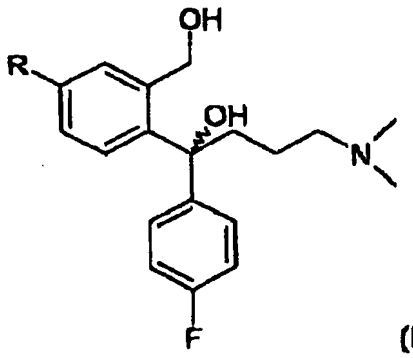
1. A process for the preparation of escitalopram having the formula



(I)

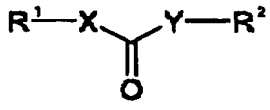
or a pharmaceutically acceptable salt thereof comprising

a) subjecting a compound of formula



(II)

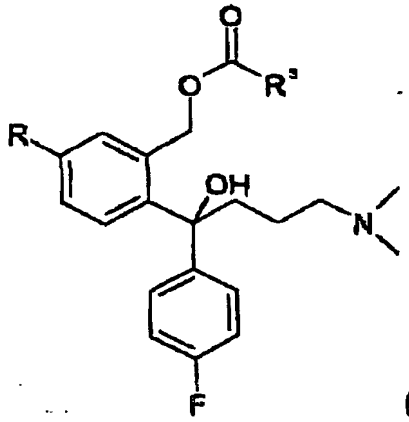
wherein R is cyano or a group which may be converted to a cyano group to enzymatic acylation in presence of a hydrolase using an acylating reagent having the formula



(III)

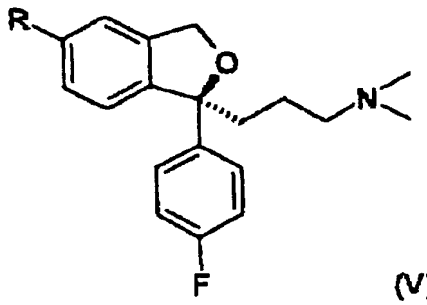
wherein X is a bond, O, S, NH or NR^0; R^0 and R^1 are independently C_{1-8}-alkyl, C_{2-8}-alkenyl or C_{2-8}-alkynyl which may optionally be substituted with C_{1-8}-alkoxy, C_{1-8}-alkylthio, halogen, C_{1-8}-alkylamino or di-(C_{1-8}-alkyl)amino, or aryl or heteroaryl; Y is O, S, O-CO, or S-CO; and R^2 is C_{1-8}-alkyl, C_{2-8}-alkenyl or C_{2-8}-alkynyl which may

optionally be substituted with C_{1-8}-alkoxy, C_{1-8}-alkylthio, halogen, C_{1-8}-alkylamino or di-(C_{1-8}-alkyl)amino, or aryl or heteroaryl; provided that X is not S or O when Y is O-CO or S-CO and X is not S when Y is S; or R^1 and R^2 together form a cyclic structure; to form a mixture of the starting material of formula (II) in either the R- or S-form and the acylated form of the other enantiomer having the formula



(IV)

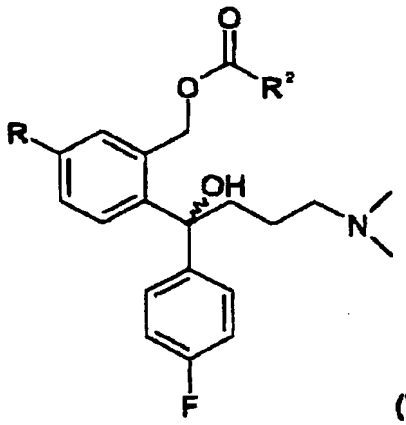
wherein R is as defined above and -CO-R^3 is a group resulting from acylation of a compound (II) with a compound of formula (III); and if R is not cyano optionally followed by conversion of the group R to a cyano group and then conversion of the S-enantiomer or formula (II) or (IV) to form a compound of formula



(V)

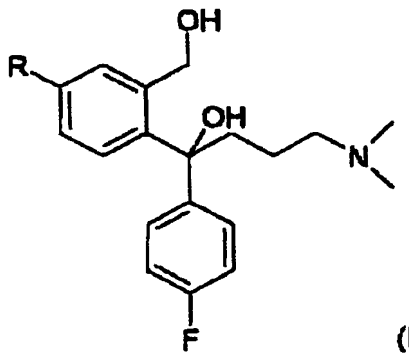
and if R is not cyano conversion of the group R to a cyano group and isolation of escitalopram or a pharmaceutically acceptable salt thereof; or

b) subjecting a compound of formula



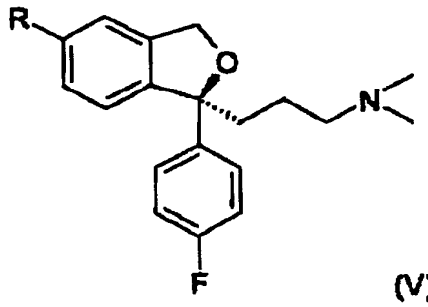
(VI)

wherein R and R^2 are as defined above; to selective enzymatic deacylation in presence of a hydrolase and water to form a mixture of deacylated compound of formula



(II)

wherein R is cyano or a group which may be converted to a cyano group in either the R- or the S-form and the acylated starting material of formula (VI) in the form of the opposite enantiomer; and if R is not cyano optionally followed by conversion of R to cyano and then conversion of the S-enantiomer or formula (II) or (VI) to a compound of formula



(V)

and if R is not cyano conversion of the group R to a cyano group and isolation of escitalopram or a pharmaceutically acceptable salt thereof.

2. The process according to claim 1 a) wherein the compounds of formula (II) and (IV) are separated before conversion of either the compound of formula (II) or the compound of formula (IV) to the compound of formula (V).

3. The process according to claim 1 a) wherein the compound of formula (II) or the compound of formula (IV) is converted to the compound of formula (V) before it is separated from the compound of formula (II) or (IV).

4. The process according to claim 1 b) wherein the compounds of formula (II) and (VI) are separated before conversion of either the compound of formula (II) or the compound of formula (VI) to the compound of formula (V).

5. The process according to claim 1 b) wherein the compound of formula (II) or the compound of formula (VI) is converted to the compound of formula (V) before it is separated from the compound of formula (II) or (VI).

6. The process according to claims 1-3 wherein the acylation of the compound of formula (II) results in a mixture of a compound of formula (II) in the S-form and the compound of formula (IV) in the R-form and the compound of formula (II) in the S-form is converted to escitalopram.

7. The process according to claims 1-3 wherein the acylation of the compound of formula (II) results in a mixture of a compound of formula (II) in the R-form and the

compound of formula (IV) in the S-form and the compound of formula (IV) in the S-form is converted to escitalopram.

8. The process according to claims 1 and 4-5 wherein the deacylation of the compound of formula (VI) results in a mixture of a compound of formula (VI) in the S-form and the compound of formula (II) in the R-form and the compound of formula (VI) in the S-form is converted to escitalopram.

9. The process according to claims 1 and 4-5 wherein the deacylation of the compound of formula (VI) results in a mixture of a compound of formula (VI) in the R-form and the compound of formula (II) in the S-form and the compound of formula (II) in the S-form is converted to escitalopram.

10. The method according to claims 1-3 and 6-7 wherein the acylation is carried out in an almost anhydrous organic solvent in presence of a hydrolase selected from PLE, HLE, PPL, CCL, PFL, PSL, CVL, MML, TVL, alfa-Chymotrypsin, Subtillisin, Trypsin, Papain, Acylase I (pig kidney or aspergillus subtilis), lipozyme™ and penicillin acylase, preferably in immobilised form.

11. The method according to claims 1, 4-5 and 8-9 wherein deacylation is carried out in water or a mixture of an organic solvent and water and a hydrolase selected from selected from PLE, HLE, PPL, CCL, PFL, PSL, CVL, MML, TVL, alfa-Chymotrypsin, Subtillisin, Trypsin, Papain, Acylase I (pig kidney or aspergillus subtilis), lipozyme™ and penicillin acylase, preferably in immobilised form.

12. The method according to claim 10 or 11 wherin the hydrolase is PPL, PLE CCL, papain, or lipozyme ™, preferably in immobilised form

13. The method according to claims 1-12 wherein R is cyano.

14. The method according to claims 1-13 wherein X is a bond.

Abstract

The present invention relates to a novel method for the preparation of escitalopram involving selective enzymatic acylation or deacylation of an intermediate in the preparation of escitalopram.